Research Article

Safety and Efficacy of Medicinal Plants Used to Manufacture Herbal Products with Regulatory Approval in Uganda: A Cross-Sectional Study

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Introduction. The Uganda National Drug Authority requires phytochemical screening, freedom from microbial contamination, and evidence of safety and efficacy of the constituent plants to register herbal products. Since Uganda has no pharmacopeia, safety, efficacy, and plant processing information are not readily available. We documented the plant materials used to manufacture products in Uganda and established evidence of their safety and efficacy and availability of monographs. *Methods*. The NDA register of herbal products was reviewed, and a product list was extracted. The herbal products were purchased from local pharmacies, and their labels were studied to identify plant ingredients and drug use. Literature was reviewed to document evidence of the safety and efficacy of the plant materials concerning manufacturer's claims. Also, the WHO and available African Pharmacopeia were searched to establish the availability of the plant monographs. *Results*. Of the 84 NDA-registered local products, only 18 were obtained from the market; 82% were indicated for respiratory tract disorders. Thirty-three plant materials were listed with *Eucalyptus globulus* Labill, being the commonest. Several *in vitro* and *in vivo* studies demonstrate efficacy, thus supporting the use of the selected plant species for empirical treatment as stated on the product label. While most plants were safe, some species such as *Albizia coriaria* Oliv. had dose-dependent toxicities that cannot be predicted in combinations. The WHO, African Pharmacopoeia, and West African Herbal Pharmacopoeia had only 16 plant monographs of the 33 plants of interest. Nevertheless, *Aloe vera* (L.) Burm.f., *Azadirachta indica* A.Juss., *Zingiber officinale* Roscoe, and *Allium sativum* L. monographs were published by all three pharmacopoeias. *Conclusions*. Preclinical evidence of safety and efficacy exists in the literature for most of the plants used to manufacture registered herbal products in Uganda. More specific bioassays and clinical trials are required for the products to provide conclusive evidence of safety and toxicity. Monographs are urgently needed for the Ugandan plants.

1. Introduction

Traditional herbal medicines have been defined as naturally occurring, plant-derived substances with minimal or no industrial processing. Such substances have been used to treat illness within local or regional healing practices [1]. More than 80% of the population within developing countries relies on herbal and other traditional medicines for primary health care [2]. These medicines are readily available, affordable, and perceived to be safe.

Traditionally, medicinal plant products have been prescribed by traditional healers within communities or self-prescribed. In this regard, assessment of efficacy and safety was based on the history of use and informal knowledge passed on from generation to generation. However, with commercialization, there is a need for scientific proof that the products are effective and safe. Various studies have demonstrated deficiencies in the quality of herbal medicines; from adulteration with conventional medicines to substitution with ineffective or harmful plant materials and contamination with soil, microorganisms, pesticides, aflatoxins, etc. [3].

Consequently, the developed world's regulatory authorities have established policies to regulate herbal and other traditional medicines. The US FDA and the EMA, for instance, have published strict requirements for market authorization of traditional methods; as such, the manufacturer has to demonstrate the efficacy and safety of the product through clinical trials, a quality assurance plan for cultivation and harvesting of the plant materials as well as protocols for good manufacturing practices [4, 5].

In contrast, traditional medicines are hardly regulated in developing countries. In a study to evaluate the regulatory framework of traditional medicines, over 60% of developing countries did not have any framework in place [6]. Following this study, the WHO published several guidelines for quality assurance of herbal medicines including, but not limited to, guidelines for registration of traditional medicines in the African region [7], guidelines for assessing the quality of herbal medicines [8], and the guidelines for good manufacturing practices herbal medicines [9].

Many African countries still have weak regulatory frameworks for traditional medicines despite these guidelines. In Uganda, for instance, there are no herbal pharmacopoeial methods for assessing the quality of herbal medicinal products. Consequently, all the locally manufactured herbal products authorized for marketing are not fully registered but rather "notified" [10]. This is because the medicines have not been evaluated fully for quality, safety, and efficacy due to regulatory and manufacturer inadequacies. To notify herbal products, the NDA considers long-standing folk use as evidence for the safety of any herbal plant material and therefore waives thorough toxicological evaluation of the product concerning the plant species used. In addition, there are no specific requirements regarding the product's efficacy. Only a report summarizing results of phytochemical screening of the plant materials used is required [11]. Once evidence for traditional use is established, specific preclinical and clinical studies to establish the safety and efficacy of the herbal products used are not a prerequisite to obtain market authorization.

Unlike in Western medicines in which pure bioactive compounds are used in pharmaceutical products, traditional medicine utilizes crude forms of whole plants or plant parts. The various plants and herbal products utilized in traditional/herbal medicine differ due to differences in climate and culture [12, 13]. Consequently, analytical methods for herbal products developed in one country are not applicable in another country. Therefore,

monographs developed by countries with established herbal medicine regulatory systems such as China and the USA cannot be applied to products that are local to a culturally and climatically different region such as sub-Saharan Africa [14].

This study aimed to document the plant raw materials used in Uganda for the manufacture of herbal products and establish a database of safety and efficacy information. This information can be added to future herbal pharmacopeia/monographs for routine use in quality assurance and quality assessment by manufacturers and regulators, respectively.

2. Methods

2.1. Study Design and Setting. This was a cross-sectional study of local herbal products registered and sold in Uganda in 2019 and a review of published literature on the safety and efficacy of the herbal raw materials between 1960 and 2021. The products were bought from the busy cities of Mbarara, Jinja, Wakiso, and Kampala. In addition, most of the manufacturers are located in this area. The pharmacies were accessed conveniently, and the only important factor was the presence of the products of interest.

2.2. Data Collection Methods. Data were collected mainly by desk review. Drug registers, product labels, and journal articles were considered. The data were collected as mentioned in the following sections.

2.2.1. Identintification of the Most Common Raw Materials and Indicated Use of the Products. The most current drug register (August 2019) of herbal medicinal products was obtained from the NDA website (https://www.nda.or.ug/drug-register-downloads/). Then, a list of the notified (partial registration to permit marketing) local herbal medicinal products was compiled. A sample of each of the products on the notified list was purchased from local pharmacies.

After the products were purchased, their labels were studied to identify the indications (use of the drug) and the active ingredients (medicinal plant materials). A database of all the herbal plant materials was then developed, and the materials were ranked according to their popularity (frequency of appearance) in the herbal medicinal products.

2.2.2. Establishment of Evidence for Efficacy and Safety of Plant Materials and Rationale for the Polyherbals. We conducted a literature review to obtain evidence of biological activity concerning the current traditional use (according to the manufacturers' labels) and safety of all the plant species used. We searched databases and search engines such as PubMed, Google Scholar, ResearchGate, Web of Science, and Scopus. The search terms consisted of the scientific plant names, pharmacological/therapeutic activity of interest, and toxicity. Only full-length articles published in English were reviewed.

2.2.3. Search for Plant Monographs Already Available. Since there are no Ugandan monographs or pharmacopeia, we were interested in finding out if monographs of the plants used in Uganda have been published in other African countries. The uses and composition of the plants were considered to be similar due to their similarity in culture and climate. We reviewed the African Pharmacopoeia 2014 [15] and the West African Pharmacopoeia 2013 [16]. Due to the absence of the monographs for most of the plants in the African Pharmacopeia, we also searched WHO monographs on selected medicinal plants volumes I–IV published between 1999 and 2009 [17–20].

3. Results and Discussions

3.1. Identification of the Most Common Plant Raw Materials and Indicated Use of the Products. By 31st March 2019, the NDA drug register had 4,148 and 214 conventional products and herbal medicinal products, respectively. All the herbal products are not fully registered but rather notified, and the majority (130) was imported, mainly from India and China. 84 locally manufactured herbal products were notified. Of these, 82% ($n = 69$) were syrups or solutions indicated for systemic treatment of upper respiratory tract disorders, such as cough, asthma, and flu. For skin infections and wound healing, the others were ointments, creams, balms, or soaps. Three products were indicated for the treatment of peptic ulcers (Table 1).

Although there were 84 locally manufactured products, we could only find 18 products in the study areas. We evaluated these products to obtain the most commonly used medicinal plant species in the formulations. Two products that did not indicate the active ingredients were eliminated.

A review of the products revealed that 33 plant species were used as raw materials. Whereas various scientific names of the plant species and/or their synonyms were used on the product information labels, we adopted the approved scientific names and their authorities according to the Kew database; Plants of the World http://www.plantsoftheworldonline.org accessed on 19th March 2021. This ensured uniformity and maintained scientific standards. We did not verify from the manufacturers if the plants indicated on the labels were the ones used to manufacture the products.

Table 1 summarizes the products found in pharmacies during data collection. Indications are as written on the product label (these are classified into major disease categories (Figure 1). Where wrongly spelled scientific plant names were found on the product labels, corrected and verified names were used instead.

Of the 33 plants listed, *Eucalyptus globulus* was by far the most used material. *E. globulus* was mentioned in 50% ($f = 9$) of the products, followed by *Aloe barbadensis, Albizia coriaria, Mangifera indica,* and *Warburgia ugandensis* tied in the third place (Figure 2). Most of the plant materials are used for self-limiting conditions, majorly to alleviate the signs and symptoms of upper respiratory tract disorders (URT) and gastrointestinal tract (GIT) disorders (Figure 1).

Figure 1 summarizes the major diseases treated by locally manufactured herbal products. Over 40% of the medicines are used to treat upper respiratory tract disorders (whooping cough, catarrh, sore throat, asthma, bronchitis, cough, flu, measles symptoms, allergic cough, smokers cough, productive cough, lung cleaning, sinusitis, common colds, rhinitis, allergic conditions, bronchial congestion, painful coughing, dry/irritating cough, nasal congestion). The rest of the products are indicated for gastrointestinal disorders (cleanses GIT, gastric ulcers, stomach ulcers, flatulence, constipation, ulcers); immune boosting (boost the immune system, antioxidant); analgesic (pain relief, painful lips); skin disorders (relief of minor skin irritations due to; insect bites, minor cuts, and minor scrapes); and mouth wash (toothache, bad odor, sensitivity, bleeding gums, cavities, tooth decay). Most of these conditions are similar to those the folk/traditional uses indicated in the pharmacopeia/monographs reviewed (Table 2).

Figure 2 shows the popularity of the plant raw materials for manufacture of herbal products. The plants were ranked based on the number of times they appear on the product label as active ingredients. Of the 33 plant raw materials, *Eucalyptus globulus* was the most common, followed by *Aloe vera* and *Albizia coriaria* in the second place, while *Albizia coriaria, Mangifera indica, Warburgia ugandensis, Azadirachta indica,* and *Zingiber officinale* tied in the third place. The rest of the plants were only mentioned once.

3.2. Establishment of Evidence for Efficacy and Safety of Plant Materials and Rationale for the (Poly) Herbal Products. Half ($n = 8$) of the surveyed locally produced herbal products were for the management of diseases of the respiratory system, with label claims such as dry, wet, and whooping cough, sore throat, bronchial asthma, nasal congestion, flu, common cold, sinusitis, and allergies. Digestive system conditions such as gastric ulcers, flatulence, and constipation are also frequently targeted. Others include immune boosters, mouth wash, antioxidants, wounds, allergies, and a lip balm. Nine of the most frequently used plant materials were reviewed in detail, for evidence of safety and efficacy in managing the conditions on the label claim. These were *A. coriaria, M. indica, A. indica, S. aromaticum, A. barbadensis, W. ugandensis, Z. officinale, A. sativum,* and *E. globulus.* The information for the rest of the plant materials is summarized in Table 3.

To establish the safety and efficacy of the plant materials, we adopted the recommendations of the WHO [7] as mentioned in the following sections.

3.2.1. General Requirements for Safety. In addition to authentication of the plant species, biological information on the safety of the plant/product should be provided. If biological evidence is lacking, data documented from long-term use should be used to assess the risk. However, the absence of toxicity data is not a guarantee of safety. Toxicity studies are required for plants and products thereof with a known toxicological risk.

Table 1: Plant materials used for the manufacture of local herbal medical products in Uganda.

No.	Product	Indication(s) as per product label	Verified scientific names (family)
1	Nana herbal mouth wash®	Toothache Bad odor Sensitivity Bleeding gums Cavities Tooth decay Antibacterial	(i) *Calendula officinalis* L. (Asteraceae) (ii) *Krameria lappacea* (Dombey) Burdet and B.B. Simpson (Krameriaceae) (iii) *Camellia sinensis* (L.) Kuntze (Theaceae) (iv) *Carica papaya* L. (Caricaceae) (v) *Eucalyptus globulus* Labill. (Myrtaceae) (vi) *Aloe vera* (L.) Burm.f. Synonym: *Aloe barbadensis* (Asphodelaceae) (vii) *Terminalia catappa* L. (Combretaceae) (viii) *Salvadora persica* L. (Salvadoraceae) (ix) *Syzygium aromaticum* (L.) Merr. and L.M.Perry (Myrtaceae) (x) *Mentha × piperita* L. (Lamiaceae)
2	Gabogola syrup®	Whooping cough, catarrh Sore throat Congestion from asthma and bronchitis	(i) *Mangifera indica* L. (Anacardiaceae) (ii) *Eucalyptus globulus* Labill. (Myrtaceae) (iii) *Albizia coriaria* Oliv. (Fabaceae)
3	Kwesiima cough mixture®	Cough Catarrh Sore throat Congestion from asthma and bronchitis	(i) *Albizia coriaria* Oliv. (Fabaceae) (ii) *Mangifera indica* L. (Anacardiaceae) (iii) *Eucalyptus globulus* Labill. (Myrtaceae) (iv) *Syzygium aromaticum* (L.) Merr. and L.M.Perry (Myrtaceae)
4	Lucas syrup®	Cough Flu Mouth sores Measles symptoms	(i) *Eucalyptus globulus* Labill. (Myrtaceae) (ii) *Warburgia ugandensis* Sprague (Canellaceae)
5	Yeco cough doctor®	Allergic cough Smokers cough Whooping cough Productive cough Flu Lung cleaning	(i) *Zanthoxylum chalybeum* Engl. (Rutaceae) (ii) *Zingiber officinale* Roscoe (Zingiberaceae) (iii) *Combretum molle* R.Br. ex G.Don (Combretaceae) (iv) *Morella kandtiana* (Engl.) Verdc. and Polhill (Myricaceae) Synonym: *Myrica kandtiana* (v) *Mangifera indica* L. (Anacardiaceae) (vi) *Allium sativum* L. (Amaryllidaceae)
6	Damaleo vera tablets®	Cleanses GIT Promotes kidney function Boost immune system	(i) *Aloe vera* (L.) Burm.f. (Asphodelaceae) Synonym: *Aloe barbadensis*
7	Muwereza herbal cough remedy	Cough Flu Sore throat Sinusitis	(i) *Azadirachta indica* A.Juss. (Meliaceae) (ii) *Aloe vera* (L.) Burm.f. (Asphodelaceae) Synonym: *Aloe barbadensis* (iii) *Zingiber officinale* Roscoe (Zingiberaceae) (iv) *Dracaena steudneri* Engl. (Asparagaceae) (v) *Albizia coriaria* Oliv. (Fabaceae)
8	Rezalin for ulcer®	Gastric ulcers Stomach ulcers Flatulence Constipation	(i) *Kigelia africana* (Lam.) Benth. (Bignoniaceae) (ii) *Tamarindus indica* L. (Fabaceae) (iii) *Azadirachta indica* A.Juss. (Meliaceae) (iv) *Entada abyssinica* A.Rich. (Fabaceae) (v) *Salvia hispanica* L. (Lamiaceae).
9	Sacco syrup®	Common colds Flu Cough Sinusitis Rhinitis Asthma Catarrh Whooping cough Allergic conditions	(i) *Morella kandtiana* (Engl.) Verdc. and Polhill (Myricaceae) Synonym: *Myrica kandtiana* (ii) *Eucalyptus globulus* Labill. (Myrtaceae) (iii) *Musa × paradisiaca* (Musaceae) (iv) *Warburgia ugandensis* Sprague (Canellaceae)
10	Replenish capsules®	Immune booster Antioxidant	(i) *Moringa oleifera* Lam. (Moringaceae)

TABLE 1: Continued.

No.	Product	Indication(s) as per product label	Verified scientific names (family)
11	Focus herbal cough syrup®	Bronchial congestion Flu associated with cough Painful coughing Dry/irritating cough Mouth sores Hiccups	(i) *Warburgia ugandensis* Sprague (Canellaceae) (ii) *Eucalyptus globulus* Labill. (Myrtaceae) (iii) *Fragaria × ananassa* (Duchesne ex Weston) Duchesne ex Rozier (Rosaceae)
12	Jenacid negus®	Ulcers	(i) *Zanthoxylum fagara* (L.) Sarg. (Rutaceae) (ii) *Solanum* spp. *(Solanaceae).* (iii) *Warbugia ugandensis* Sprague (Canellaceae) (iv) *Curcuma longa* L. (Zingiberaceae) (v) *Allium sativum* L. (Amaryllidaceae)
13	Witch hazel®	Relief of minor skin irritations due to insect bites Minor cuts, minor scrapes	(i) *Hamamelis virginiana* L. (Hamamelidaceae)
14	Phycof cough syrup®	Dry, wet, and whooping cough Sore throat Bronchial asthma Relieving fever Nasal congestion	(i) *Zingiber officinale* Roscoe (Zingiberaceae) (ii) *Curcuma longa* L. (Zingiberaceae) (iii) *Eucalyptus globulus* Labill. (Myrtaceae) (iv) *Mentha × piperita* L. (Lamiaceae) (v) *Cymbopogon citratus* (DC.) Stapf (Poaceae) (vi) *Citrus limon* (L.) Osbeck (vii) *Tinospora sinensis* (Lour.) Merr. (Menispermaceae). Synonym: *Tinospora cordifolia* (viii) *Albizia coriaria* Oliv. (Fabaceae) (ix) *Acorus calamus* L. (Acoraceae) (x) *Xanthium strumarium* L. (Astaraceae)
15	Princess aloe lip balm®	Dry, cracked, and painful lips	(i) *Aloe vera* (L.) Burm.f. (Asphodelaceae) Synonym: *Aloe barbadensis* (ii) *Azadirachta indica* A.Juss. (Meliaceae)
16	Princess pain balm®	Pain relief	(i) *Eucalyptus globulus* Labill. (Myrtaceae) (ii) *Cinnamomum verum* J.Presl (Lauraceae) Synonym: *Cinnamomum zeylanicum*

3.2.2. General Requirements for Efficacy. Generally, proof of the efficacy of traditional medicine is determined by indications for use (concerning biological evidence) and testimony by physicians, traditional practitioners, and patients after a long duration of use. Appropriate clinical trials should be conducted for cases where no history of use or biological information has been documented. The WHO has published guidelines for the clinical study of traditional medicines in the WHO African region [79].

To ensure reproducibility of efficacy, the preparation of medicines should be standardized so that each batch contains a defined amount of the active ingredients.

Information on safety and efficacy can be obtained from scientific literature, national or international pharmacopeia, and WHO monographs for selected plant materials.

3.2.3. Albizia coriaria Oliv. (Fabaceae). Albizia coriaria is used in many local herbal preparations to manage upper respiratory tract infection (URTI) and other infections in Uganda [21, 80]. Products containing *A. coriaria* include Gabogola syrup®, Kwesiima cough mixture®, Muwereza herbal cough remedy®, and Phycof cough syrup®. Upper respiratory tract infections are typically caused by the rhinovirus, adenovirus, influenza, enterovirus, and respiratory

syncytial virus [81]. Bacteria cause about 15% URTI, and the most implicated bacterium is *Streptococcus pyogenes*. URTI causes a variety of diseases with overlapping presentations, including acute bronchitis, influenza, rhinitis, pharyngitis, tonsillitis, laryngitis, and other respiratory distress syndromes. Symptoms of URTI commonly include cough, sore throat, runny nose, nasal congestion, headache, low-grade fever, facial pressure, sneezing, malaise, and myalgias. Most viral infections are self-limiting [81]. The goal of treatment is symptom relief, and in case of bacterial infections, anti-infectives can be used [82]. Therefore, for the effective management of URTI, the medication should possess one or more of the following activities: antiviral, antibacterial, anti-inflammatory, expectorant, and decongestant.

Bioactive compounds such as lupeol, lupenone, betulinic acid, and catechin extracted using ethyl acetate from the stem bark of *A. coriaria* had activity against *Pseudomonas aeruginosa* and *Escherichia coli* [83]. These bacteria are, however, not commonly implicated in the causation of URTI. No specific studies were evaluating the activity of the bark of *A. coriaria* against Gram-positive cocci, which are the causative agents of URTI. Lupeol has anti-inflammatory activity [84]. Treatment with lupeol reduces mucus secretion and overall lung inflammation in a murine model [85]. The antiviral activity of lupenone is selective. Lupenone exhibits

a strong viral plaque inhibitory effect against herpes simplex virus (HSV)-1 and HSV-2 and inhibits African swine fever virus [86], but none of these viruses cause URTI. When studied in experimentally induced polymicrobial sepsis in mice, betulinic acid exhibited a protective effect on the lungs by inhibiting the production of inflammatory mediators. In another study, betulinic acid showed anti-inflammatory and antioxidant properties that protect the lungs against lipopolysaccharide-induced lung inflammation in rats [87].

Herbalists use *A. coriaria* in very small quantities in polyherbal preparations and boil it for several hours because of its known toxicity. Not surprisingly, the DMSO and ethanol extracts of *A. coriaria* were highly cytotoxic to the human glioblastoma U87.CD4.CXCR4 cells ($CC_{50} = 6.4$ and $<4\,\mu g/ml$ respectively) [57]. *Albizia* spp. has a toxic compound, 4-methoxypyridoxine, which antagonizes vitamin B_6 [88].

Other *Albizia* species have shown different toxicities, including several central nervous system disturbances and other effects on the cardiovascular and respiratory systems. For instance, seed methanolic extracts of *Albizia greveana* and *Albizia bernieri* are toxic to mice with LD_{50} of 1.13–2.3 and 52 mg/kg body weight, respectively, the former being more than one toxic [89]. However, the methanol and aqueous extracts of *A. coriaria* have been shown to have very low cytotoxicity ($CC_{50} > 500\,\mu g/ml$) against human embryonic lung fibroblast (HELF) cells [90]. In contrast, the methanol, ethanol, ethyl acetate, and diethyl ether extracts of *A. coriaria* were not toxic to the human keratinocyte cell line (HaCaT) $IC_{50} > 512$ [91].

There is scientific evidence for the usefulness of *A. coriaria* in the symptomatic management of respiratory tract conditions. However, specific studies need to be done to assess URTI activity against the causative organisms. Specific toxicity studies on the bark of *A. coriaria* need to be done to conclude on the safety of the plant.

3.2.4. Mangifera indica L. (Anacardiaceae).

Mangifera indica is also used in many preparations for URTI management from the survey, including Gabogola syrup®, Kwesiima cough mixture®, and Yeco cough doctor®. *M. indica* is widely used to manage various infections and as an immune booster in Uganda [80]. Various pharmacological investigations have been carried out to explore the therapeutic potential of the phytochemicals in different plant parts of *M. indica* [92]. However, for the management of URTI, the antiviral, antibacterial, anti-inflammatory, expectorant, and decongestant activities of *M. indica* are important. Extracts from the fruit pulp of *M. indica* possess antiviral activity against influenza virus H9N2 and chicken embryo fibroblast (CEFs) with low cytotoxicity [93]. Mangiferin, extracted from the leaves of *M. indica*, inhibited herpes simplex virus 2 (HSV-2) replication but did not directly inactivate the virus [94]. Extracts from the stem bark of *M. indica* have some bacteriostatic activity against *S. aureus* albeit lower than the activity of the positive control used, ampicillin [95]. Alok et al. [96] demonstrated the antibacterial effects of the aqueous kernel extracts of two

M. indica varieties (Bagnapalli and Senthura) from Tamil Nadu (India) against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Acetone, methanol, and water extracts of the leaves on *M. indica* exhibited lower antibacterial activity against *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *Bacillus cereus*, *E. coli*, *P. aeruginosa*, *Proteus mirabilis*, *Salmonella typhi*, and *Shigella flexneri* using the agar well (cup plate) diffusion method than gentamicin and erythromycin [97].

A toxicological evaluation of *M. indica* leaf extract containing 60% mangiferin revealed a no-observed-adverse-effect level in male and female rats at 2000 mg/kg body weight/day. Additionally, no evidence of genotoxicity was found in a bacterial reverse mutation test [98]. *In vivo* acute toxicological studies of the stem bark aqueous extract of *M. indica* in rats and mice showed no lethality at the limit dose of 2,000 mg/kg body weight and no adverse effects when given by oral or dermal administration. Deaths occurred when the extract was administered intraperitoneally at 200 mg/kg in mice [99]. *M. indica* extracts were nonirritating on rabbits' skin and ocular and rectal mucosa [99].

There were no specific studies found evaluating the expectorant and decongestant activities of *M. indica*. Overall, the antiviral and antibacterial activities of various parts of the plant support its use in URTI management.

3.2.5. Azadirachta indica A. Juss. (Meliaceae).

Azadirachta indica (neem tree) is used in the following products: Muwereza herbal cough remedy®; Princess aloe lip balm®, a lip balm®; and Rezalin for ulcer®, a syrup for management of gastric ulcers, flatulence, and constipation. To support its use in a cough remedy, *A. indica* should possess expectorant, decongestant, antiviral, and/or antibacterial activities [82].

The bark extract of *A. indica* significantly blocked HSV-1 entry into cells at concentrations ranging from 50 to 100 $\mu g/ml$ [100]. The methanolic extract fraction of leaves of *A. indica* is virucidal against Coxsackie virus B-4 and interfered with an early event in the viral replication [101]. Thus, the antiviral activity has been demonstrated but not in the viruses known to commonly cause URTI, such as the rhinovirus, adenovirus, influenza virus, enterovirus, and respiratory syncytial virus.

The bark, leaf, seed, and fruit extracts of *A. indica* showed a concentration-dependent antibacterial activity against bacteria isolated from an adult mouth [102]. The ethanolic extract of neem twigs, barks, and leaves are bactericidal against *Streptococcus mutans* [103].

The methanol fraction of neem oil possesses bactericidal activity against 9 strains of *Helicobacter pylori*, the causative agent of gastric ulcers [104]. The extract's minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against the *H. pylori* strains ranged between 25 and 51 $\mu g/ml$ and 43–68 $\mu g/ml$, respectively. The bactericidal activity was time- and concentration-dependent [104]. This evidence supports the use of neem in Rezalin® syrup to manage ulcers.

The wound-healing effect of neem could be beneficial in the lip balm. The water extract of the stem bark of *A. indica*
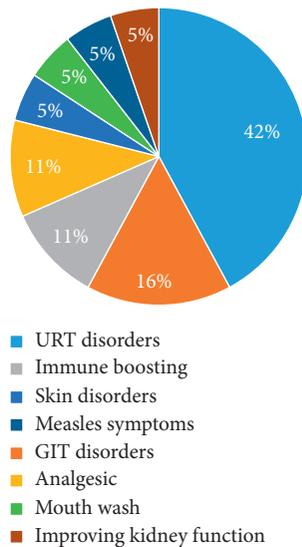
Figure 1: Summary of diseases treated by the herbal medicinal products manufactured in Uganda.

promoted wound healing in mice by increasing the rate of wound contraction and levels of hydroxyproline, DNA and protein content, and nitric oxide compared with the vehicle control group. These effects promote wound healing through increased inflammatory response and neovascularization [105].

Neem oil poisoning is rare in adults. However, one such case was reported in an adult male who presented with vomiting, seizures, metabolic acidosis, and toxic encephalopathy [106]. The patient had a complete recovery from symptomatic management. *In vivo* evaluation of acute toxicity of water extracts of *A. indica* leaves and seeds in rats revealed an LD_{50} of 6.2 and 9.4 ml/kg, respectively [107].

There is evidence to support the use of *A. indica* in URTI management, gastric ulcers associated with *H. pylori* infection, and wound healing. The use of the oil has the potential to cause adverse events.

3.2.6. Syzygium aromaticum (L.) Merr. and L.M.Perry (Myrtaceae).

S. aromaticum (clove) was found in Kwesiima cough mixture® (a preparation for management of URTI) and Nana herbal mouth wash® (for management of toothache, tooth decay, sensitivity, bleeding gums). The antibacterial, anti-inflammatory, analgesic, anesthetic, and antiviral activities of *S. aromaticum* are important for these applications.

S. pyogenes and *S. mutans* are the most common causes of bacterial URTI and tooth decay, respectively [108]. The essential oil extracted from the dried flower buds of clove has antiseptic, anti-inflammatory, analgesic, and anesthetic activities [109]. This supports its common use in dentistry. Furthermore, eugenol, the main constituent of clove essential oil, showed an antinociceptive effect in a dose-dependent manner as measured in the acetic acid-induced writhing test in mice, with the effect lasting at least 30 minutes [110].

The methanolic extract of *S. aromaticum* has potent inhibitory activity against both dental caries pathogens with MIC of 0.2 mg/ml. In addition, *S. aromaticum* bud essential oil was active against *S. mutans* at 0.05 mg/ml [111]. Furthermore, the antibacterial activity of clove has been demonstrated in *S. aureus, Pseudomonas aeruginosa, E. coli, S. pyogenes, Corynebacterium species, Salmonella species,* and *Bacteroides fragilis* [112].

An *in vitro* study demonstrated cytotoxic properties of clove oil and eugenol toward human fibroblasts and endothelial cells. Clove oil was highly cytotoxic at concentrations as low as 0.03% (v/v) with up to 73% of this effect attributable to eugenol [113]. Moreover, eugenol produces local irritative and cytotoxic effects and hypersensitivity reactions when in contact with soft tissues [114]. However, Vijayasteltar et al. [115] evaluated the subchronic toxicity of the standardized polyphenolic extracts of clove buds in Wister rats and showed a no-observed-adverse-effect level at 1000 mg/kg bodyweight/day. This study showed that administration of the extracts did not result in any toxicologically significant changes in clinical/behavioral observations, ophthalmic examinations, body weights, organ weights, feed consumption, urinalysis, hematology, and clinical biochemistry parameters when compared with the untreated control group of animals. Also, no genotoxicity was observed with the extract rather exhibiting significant antimutagenic potential against the known mutagens: sodium azide, NPD, tobacco, and 2-acetamidoflourene.

The antibacterial, anti-inflammatory, analgesic, and anesthetic activities of *S. aromaticum* provide evidence for its value in managing URTI and dental conditions.

3.2.7. Aloe barbadensis (L.) Burm.f. (Asphodelaceae).

Aloe barbadensis is a constituent of Nana herbal mouth wash®, Damaleo vera tablets® (for cleansing the GIT, promotion of kidney function, and boosting the immune system), Muwereza herbal cough remedy®, and Princess aloe lip balm®.

A wound dressing gel containing acemannan, extracted from the internal leaf aloe gel, reduced radiation-induced skin reactions in mice when applied daily for at least 2 weeks, beginning immediately after irradiation [116]. Furthermore, the extracts of crude *A. barbadensis* gel prevent suppressing the induction of T cell-mediated responses such as contact and delayed-type hypersensitivity caused by cutaneous exposure to ultraviolet light [117]. This effect is attributed to aloe oligosaccharides that prevent ultraviolet-induced suppression of delayed-type hypersensitivity by reducing keratinocyte-derived immunosuppressive cytokines such as interleukin-10. This evidence supports the use of aloe extracts in lip balm.

Acemannan from *A barbadensis* extract stimulated macrophage production of monokines, including interleukin-1 and tumor necrosis factor, resulting in the initiation of immune attack, necrosis, and regression of implanted sarcomas in mice [118]. In another study, *A. barbadensis* stimulated cellular and humoral immune responses in rabbits following immunization against myxomatosis [119].
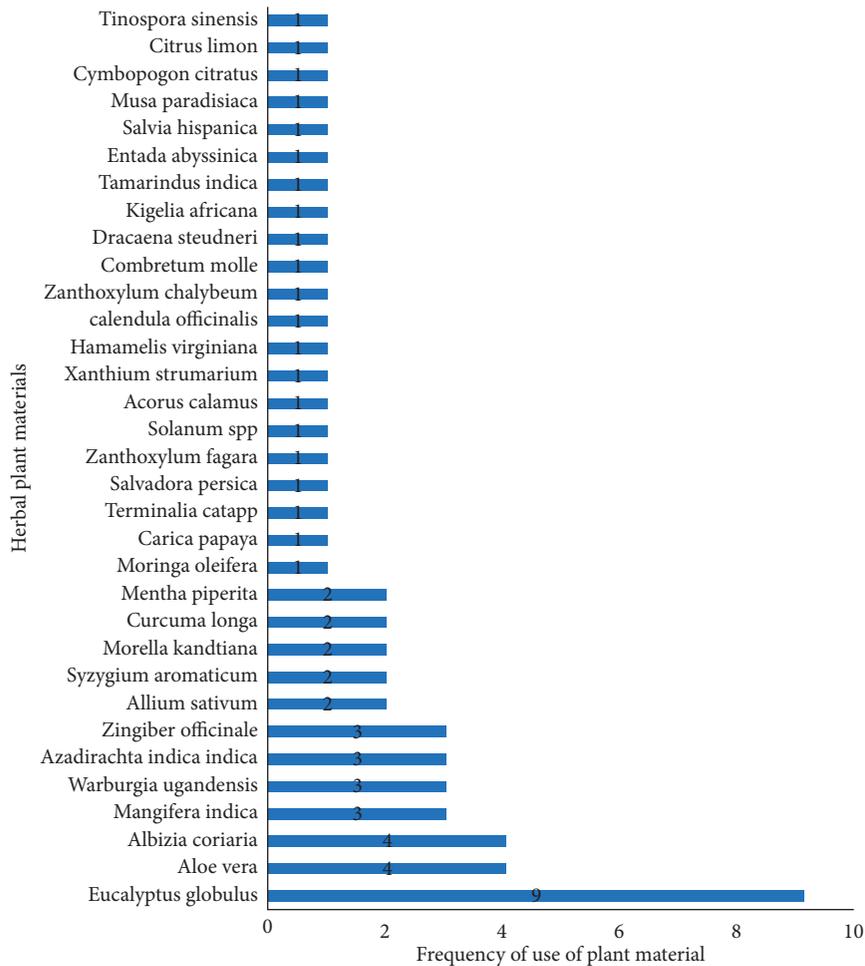
FIGURE 2: Popularity of herbal materials used to manufacture local herbal medical products in Uganda.

Furthermore, aloe extracts enhanced the ability of broiler chickens to mount a humoral immune response when challenged with Newcastle disease virus [120]. These studies support the use of *A. barbadensis* extract to boost the immune system.

Emodin, an anthraquinone prepared from aloin, was shown to inactivate herpes simplex virus type 1 and type 2, varicella-zoster virus, pseudorabies virus, and influenza virus, not adenovirus and rhinovirus. Electron microscopic examination of the anthraquinone-treated herpes simplex virus demonstrated that the envelopes were partially disrupted [121]. This antiviral activity is important in the management of URTI.

Aloe emodin is also a known stimulant laxative [122], and this could be the basis of the use of *A. barbadensis* in Damaleo vera tablets for cleansing the GIT.

The generative changes in the kidney tissue were significantly reduced in diabetic rats treated with glibenclamide and aloe leaf gel and pulp extracts compared with the untreated group [123]. The treated group also had decreased serum urea and creatinine levels in comparison with diabetic controls. Among the diabetic rats, kidney lipid peroxidation levels were lower in those received aloe extracts than those who received glibenclamide alone. These findings suggest a protective effect of *A. barbadensis* on mild damage caused by type-II diabetes on kidney tissue and support its use in Damaleo vera tablets.

Several single case reports have been published on the toxicity of *A. barbadensis* in humans. Some include massive intraoperative bleeding after consumption of *A. barbadensis* tablets [124], acute renal failure [125], severe vomiting [126], acute hepatitis [127], and Henoch-Schonlein purpura [128]. Ernst [129] reported on the hypersensitivity and allergic reactions due to *A. barbadensis*. In another study, rats fed aloe whole-leaf powder for 90 days showed the adverse effect level to be 2 g/kg BW [130]. Aloe inner leaf gel rich in high-molecular-weight fibers and soluble polysaccharides is cytotoxic to the human intestinal cell line Caco-2 ($CC_{50} = 1$ g/l), even at concentrations below the recommended dose for human consumption [131]. Processing of aloe inner leaf gel or aloe leaf extract by filtration through diatomaceous earth and activated carbon reduces their cytotoxicity and improves their immunomodulatory activity [131].

Literature supports the use of aloe extracts for cosmetic purposes, boosting the immune system, and management of URTI and constipation. However, studies also show that aloe extracts can be toxic, although processing can reduce such toxicities.

TABLE 2: Availability of plant monographs in African- and WHO-published pharmacopoeia/monographs.

No.	Plant material (manufacturer use in Uganda)	African Pharmacopoeia, 2014 [15] (i) Part(s) of plant used (ii–iv) Similar traditional use	West African Herbal Pharmacopoeia, 2013 [16] (i) Part(s) of plant used (ii–iv) Similar traditional use	WHO monographs (vol I–IV) (i) Part(s) of plant used (ii–iv) Similar traditional use
1.	*Eucalyptus globulus* Labill. (i) Mouth wash (ii) URT disorders (iii) Analgesic	(i) Oil (ii) Astringent, antiseptic (iii) Asthma	No monograph	(i) Oil (ii) Dental caries, ulcers of the skin (iii) Catarrh and coughs, sinusitis
2.	*Aloe vera (L.)* Burm.f. (i) Wound healing (ii) Mouth wash (iii) Immune booster (iv) GIT disorders (v) Promote kidney function	(i) Dried juice (ii) Cathartic	(i) Decoction, juice, dried juice (ii) Dermatitis, thermal and sunburns (iii) Cold (iv) Peptic ulcer	(i) Dried juice, gel (ii) Seborrhoeic dermatitis, minor wounds and inflammatory skin disorders, haemorrhoids (iii) Peptic ulcers
3.	*Albizia coriaria* Oliv.	No monograph	No monograph	No monograph
4.	*Mangifera indica* L.	No monograph	No monograph	No monograph
5.	*Warburgia ugandensis* Sprague	No monograph	No monograph	No monograph
6.	*Azadirachta indica* A.Juss. (i) URT disorders, (ii) Wound healing	(i) Leaves (ii) Inflammatory agent	(i) Leaves, stem bark, seeds (ii) Cough, (iii) Skin disorders, boils, ulcers, eczema	(i) Leaves (ii) Asthma (iii) Wounds, bruises, allergic skin itching due to varicella, psoriasis, scabies, smallpox, warts
7.	*Zingiber officinale* Roscoe (i) URT disorders	(i) Rhizome (ii) No similar traditional use	(i) Rhizome (ii) cough, colds, flu, asthma	(i) Rhizome (ii) Cold and flu, anti-inflammatory agent
8.	*Allium sativum* L. (i) GIT disorders (peptic ulcers) (ii) URT disorders	(i) Bulb (ii) Antimicrobial	(i) Bulb, oil from bulb (ii) Antidiarrheal, stomachic, dysentery (iii) Expectorant, broad spectrum antibiotic	(i) Bulb (ii) Dysentery, ulcers, carminative, cholera, colic (iii) Asthma, expectorant, bronchitis
9.	*Syzygium aromaticum* (L.) Merr. and L.M.Perry (i) Mouth wash (ii) URT disorders	(i) Flower buds, oil (ii) Toothache	No monograph	(i) Flower buds (ii) Mouthwashes, treatment of toothache, bleeding gums, and minor infections of the mouth (iii) Sore throats and coughs associated with the common cold, asthma
10.	*Morella kandtiana* (Engl.) Verdc. and Polhill	No monograph	No monograph	No monograph
11.	*Curcuma longa* L. (i) GIT disorders (Gastric ulcers) (ii) URT disorders	No monograph	No monograph	(i) rhizome (ii) Peptic ulcers, diarrhea (iii) Coughs
12.	*Mentha piperita* L. (i) URT disorders (ii) Mouth wash	(i) Leaves, oil No similar traditional use	No monograph	(i) Essential oil (ii) Symptomatic treatment of catarrh and coughs
13.	*Moringa oleifera* Lam. (i) Immune booster (ii) Antioxidant	(i) Seeds (ii) Wound healing, (iii) Antioxidant, anti-inflammatory	(i) Leaves, flower, fruit, root, seed (ii) Supplements	No monograph

TABLE 2: Continued.

No.	Plant material (manufacturer use in Uganda)	African Pharmacopoeia, 2014 [15] (i) Part(s) of plant used (ii–iv) Similar traditional use	West African Herbal Pharmacopoeia, 2013 [16] (i) Part(s) of plant used (ii–iv) Similar traditional use	WHO monographs (vol I–IV) (i) Part(s) of plant used (ii–iv) Similar traditional use
14.	*Carica papaya* L. (i) Mouth wash	(i) Fresh fruits (ii) GIT disorders	(i) Leaf, fruit or root, seed (ii) Dental caries	No monograph
15.	*Terminalia catappa* L.	No monograph	No monograph	No monograph
16.	*Salvadora persica*	No monograph	No monograph	No monograph
17.	*Zanthoxylum fagara* (L.) Sarg.	No monograph	No monograph	No monograph
18.	*Solanum* spp.	No monograph	No monograph	No monograph
19.	*Acorus calamus* L.	No monograph	No monograph	No monograph
20.	*Xanthium strumarium* L.	No monograph	No monograph	No monograph
21.	*Hamamelis virginiana* L. (i) Skin ulcers, (ii) Skin irritations	No monograph	No monograph	(i) Leaves and bark (ii) Neuralgia, nosebleeds
22.	*Calendula officinalis* L. (i) Mouth wash	No monograph	No monograph	(i) Ligulate florets and composite flowers (ii) Superficial cuts, minor inflammations of the skin and oral mucosa, gastritis.
23.	*Zanthoxylum chalybeum* Engl.	No monograph	No monograph	No monograph
24.	*Combretum molle* R.Br. ex G.Don	No monograph	No monograph	No monograph
25.	*Dracaena steudneri* Engl.	No monograph	No monograph	No monograph
26.	*Kigelia africana* (Lam.) Benth.	No monograph	No monograph	No monograph
27.	*Tamarindus indica* L. (i) GIT disorders	(i) Fruits and seeds (ii) Laxative	No monograph	No monograph
28.	*Entada abyssinica* A.Rich.	No monograph	No monograph	No monograph
29.	*Salvia hispanica* L.	No monograph	No monograph	No monograph
30.	*Musa paradisiaca*	No monograph	No monograph	No monograph
31.	*Cymbopogon citratus* (DC.) Stapf. (i) URT disorders	(i) Herb (ii) No similar traditional use	(i) Leaf, flower (ii) Anticatarrhal and antirheumatic	No monograph
32.	*Citrus limon* (L.) Osbeck (i) URT disorders	Plant called *Citrus limonum* Risso (i) Pericarp (fresh or dry) (ii) No similar traditional use	No monograph	No monograph
33.	*Tinospora sinensis* (lour.) Merr.	No monograph	No monograph	No monograph

3.2.8. Warburgia ugandensis Sprague. (Canellaceae). *W. ugandensis* is a constituent of herbal preparations including Lucas syrup®, Sacco syrup®, Focus herbal cough syrup® used in the management of URTI, and Jenacid negus® for the management of gastric ulcers.

The water extracts of *W. ugandensis* elicited antimicrobial activity against *E. coli* and *S. aureus* in the agar well assay, with higher activity against *S. aureus* than *E. coli*. This activity was only detectable at high concentrations of the extract, i.e., up to 50 mg/ml of crude extract [132]. In another study, the crude and petroleum ether extracts of *W. ugandensis* leaves exhibited antimicrobial activity against *S. boydii* and *S. aureus* [133]. The biological activities of the plant are attributed to the drimane and colorotane sesquiterpenoids, including polygodial, warburganal, muzigadial, mukaadial, and ugandensial, as well as flavonoids

and other compounds [134, 135]. The sesquiterpene muzigadial isolated from the ethyl acetate extract of the stem bark of *W. ugandensis* was the main antibacterial agent (IC$_{50}$ = 12.5 μg/ml) against both *S. aureus* and *Bacillus subtilis* [136].

Specific antiviral activity studies could not be found to assess the importance of *W. ugandensis* in the management of viral URTI. Its usefulness in the management of peptic ulcer disease could also not be established from the literature review. Other reported pharmacological activities of *W. ugandensis* backed by some scientific evidence include antifungal activity, antimycobacterial activity, anti-inflammatory and antioxidant properties, molluscicidal, antifeedant, antiplasmodial, cytotoxic, anthelmintic, and antileishmanial activities [135]. The diethyl ether extract of *W. ugandensis* has anti-inflammatory effects and inhibited

Table 3: Evidence of efficacy and safety for herbal materials used for manufacture of medicinal products in Uganda.

No.	Plant material	Use of product (containing the material) according to the label	Evidence of efficacy related to product label claim; mechanism of action	Evidence of safety
10.	*Morella kandtiana* (Engl.) Verdc. and Polhill	URT disorders	Root extracts exhibited low inhibitory effects on the growth of *Acinetobacter baumannii* CDC-0033 (IC$_{50}$: 128 μg/ml; MIC: >256 μg/ml) and moderate effects on *Pseudomonas aeruginosa* AH-71 (IC$_{50}$: 32 μg/ml; MIC: 256 μg/ml) [21]	Very low toxicity to human HaCaT cells IC$_{50}$ = 512 μg/ml [21].
11.	*Curcuma longa* L.	Gastric ulcers	*C. longa* extract inhibits gastric acid secretion by competitively blocking H(2) histamine receptors [22]	The extract was safe and efficacious in the treatment of painful knee osteoarthritis in a randomized placebo-controlled trial [23].
		URT disorders	Curcumin reduced ethanol-induced gastric lesions and significantly increased gastric blood flow and plasma gastrin levels in a dose-dependent manner. This involves endogenous PG, NO, gastrin, and CGRP released from sensory nerves due to activation of the vanilloid TRPV1 receptor. This protective effect can be attributed to the inhibition of HIF-1a and Cdx-2 expression and the activation of HO-1 and SOD 2 expression [24]	
12.	*Mentha piperita* L.	URT disorders	A spray containing essential oils of five plants including *M. piperita* caused significant and immediate improvement in symptoms of upper respiratory ailment in a randomized clinical trial [25]	Short-term and subchronic oral studies reported cyst-like lesions in the cerebellum in rats given high doses of peppermint oil (>200 mg/kg/day). Peppermint oil contains the hepatotoxin pulegone. Isolated clinical cases of irritation and/or sensitization to peppermint oil and/or its constituents have been reported [26].
		Mouth wash		
13.	*Moringa oleifera* Lam.	Immune booster	The methanolic leaf extract caused significant immune-stimulatory effects on both cell-mediated and humoral immune systems in the Wistar albino rats [27]. The ethanolic and saline extracts contain antioxidants [28]. The leaf extract increased the antioxidant activity of glutathione (186%), superoxide dismutase (97.8%) and catalase (0.177%) [29].	The leaves are genotoxic at supra-supplementation levels of 3000 mg/kg BW but are safe at levels ≤1000 mg/kg BW in rats (LD$_{50}$ = 1585 mg/kg) and thus nontoxic [30].
		Antioxidant		
14.	*Carica papaya* L.	Mouth wash	A randomized, single-blind parallel-design study showed the leaf extract dentifrice/mouthwash provided an efficacious and natural alternative to sodium lauryl sulfate-free dentifrice ± essential oil-containing mouthwash in reducing interdental gingival inflammation [31]	The leaf extract is safe as shown in subacute oral toxicity tests in Sprague Dawley rats at up to 2 g/kg, (14 times the levels used in traditional medicine in Malaysia [32, 33]). Short-term leaf consumption in adults is generally safe though cautioned in pregnancy and liver impairment [34]
15.	*Terminalia catappa* L.	Mouth wash	The leaf aqueous and methanol extract demonstrated antibacterial activity against different bacterial strains [35]	The aqueous leaf extract is relatively nontoxic to the heart in subacute toxicity studies [36]
16.	*Salvadora persica* L.	Mouth wash	*S. persica* extract caused significant reduction in the plaque score and cariogenic bacterial count, but the score was lower than the positive control chlorhexidine mouthwash [37].	The aqueous and ethanolic extracts were not toxic to mice at doses of up to 1200 mg/kg [38]
17.	*Zanthoxylum fagara* (L.) Sarg	Gastric ulcers	No specific data for *Z. fagara*.	No specific data for *Z. fagara*

TABLE 3: Continued.

No.	Plant material	Use of product (containing the material) according to the label	Evidence of efficacy related to product label claim; mechanism of action	Evidence of safety
18.	Solanum spp.	Gastric ulcers	Methanolic, alcoholic, and aqueous extracts of Solanum species increase gastric mucus secretion and reduce HCl secretion [39], thus acting as a mechanical barrier and protecting the mucosa [40]	Solanum species contain toxic glycoalkaloids including solanine, chaconine, and solasodine. Toxicity manifests as gastroenteritis, weakness, excessive salivation, dyspnea, tremors, paralysis, prostration, and death [41]. Boiling reduces toxicity.
19.	Acorus calamus L.	URT disorders	Showed antibacterial activity against Enterobacter aerogenes and S. aureus and Proteus mirabilis [42].	The hydroalcoholic extract of A. calamus is nontoxic but at high dose produces mild but acceptable toxicity potential [43]
20.	Xanthium strumarium L.	URT disorders	Anti-inflammatory activity through inhibition of IFN-γ lipopolysaccharide-induced NO production and TNF-α production and analgesic activity [44] and inhibits histamine, interleukins, and TNF α, which are important in allergic rhinitis [45, 46],	A decoction caused hepatic injury, symptomatic hypoglycemia, and seizures 7 days after administration [47]. Extracts can induce in vitro DNA damage at cytotoxic concentrations in vitro [48] X. strumarium contains the toxic compounds atractyloside, carboxyatractyloside, and 4′-desulphate-atractyloside, which XSF induced significant cytotoxic effects in both L-02 and BRL liver cell lines [49]
21.	Hamamelis virginiana L.	Skin ulcers / Skin irritations	A shampoo from H. virginiana improved subjective manifestations of skin irritation [50]. Extracts have antifungal and antibacterial effects against Candida albicans and S. aureus [51]	Did not cause any toxicity or deaths in rabbits when administered through the rectum at 300 mg/kg for 28 days [52]
22.	Calendula officinalis L.	Mouth wash	A randomized controlled clinical study showed that a flower extract mouthwash of C. officinalis could be effective on reducing the intensity of radiation-induced oropharyngeal mucositis in patients with head-and-neck cancer [53]. In another randomized controlled study, C. officinalis mouth wash was shown to be effective in treating gingivitis by significantly reducing the plaque and gingival index [54]	Acute and subchronic toxicity studies indicated that the extracts of C. officinalis have low toxicities in Wistar rats [55]
23.	Zanthoxylum chalybeum Engl.	URT disorders	The essential oil exhibited strong antibacterial activities against S. typhi, S. agalactia, S. aureus, and E. coli [56]	The ethanol extract was weakly cytotoxic ($CC_{50} = 231.0\,\mu g/ml$), whereas the DMSO extract was moderately cytotoxic ($CC_{50} = 39.8\,\mu g/ml$) to U87CD4CXCR4 cells [57]. The methanol, ethanol, ethyl acetate, and diethyl ether extracts were not toxic to human keratinocyte cell line (HaCaT) $IC_{50} > 512$ [21]
24.	Combretum molle R.Br. ex G.Don	URT disorders	C. molle has antibacterial activity. The MIC and MBC values ranged from 2.5 mg/ml to 5.0 mg/ml [58]	The aqueous leaf extract is moderately toxic when given to rats intraperitoneally at doses up to 8000 mg/kg [59].
25.	Dracaena steudneri Engl.	URT disorders	The leaves contain flavones and flavanones that inhibits proinflammatory cytokine release [60]	No specific data available

TABLE 3: Continued.

No.	Plant material	Use of product (containing the material) according to the label	Evidence of efficacy related to product label claim; mechanism of action	Evidence of safety
26.	*Kigelia africana* (Lam.) Benth.	Gastric disorders (ulcers, flatulence, constipation)	The aqueous leaf possesses antiulcer potential with protective and curative effects against gastric lesion [61]. *K. africana* at a concentration of 450 mg/kg BW gave the best results with a significant decrease in ulcer index (0.67 ± 0.16) on aspirin-induced ulcerogenic animals compared with 3.0 for the reference drug (cimetidine at 300 mg/kg) and control with 1.67 ± 0.27 [62]	The aqueous bark extract was safe in rats up to 5 g/kg [63]. At a higher dose of 6400, the extract was toxic in rats [64]
27.	*Tamarindus indica* L.	Gastric disorders (ulcers, flatulence, constipation)	The seed extract showed a dose-dependent protective effect on animal peptic ulcer models [65]. The leaf extract exhibited antiulcerogenic and ulcer-healing properties in rats [66].	Even at high concentrations, the extract administered to rats was still safe compared with the 5% concentration usually present in juice consumed by humans [67]
28.	*Entada abyssinica* A.Rich.	Gastric disorders (ulcers, flatulence, constipation)	Contains entadanin, which possess strong antibacterial activity against *Salmonella typhimurium* with the lowest MIC of 1.56–3.12 μg/ml [68]	The IC_{50} values for the different active compounds ranged from 0.48 to 2.87 μg/ml in the DPPH assay, from 2.53 to 17.04 μg/ml in the ABTS assay, and from 1.43 to 103.98 μg/ml in the FRAP assay. The compounds were less toxic than the positive control (LC_{50} values 22.42 to 80.55 μg/ml) in Vero cells, suggesting relative lack of cytotoxicity [68].
29.	*Salvia hispanica* L.	Gastric disorders (ulcers, flatulence, constipation)	Chia seeds caused a significant decrease in symptoms of the constipation symptoms in the third week of treatment [69]	Chia seeds are safe as a novel food [70]
30.	*Musa paradisiaca*	URT disorders	Both the ethanol aqueous extracts showed antibacterial activity against *S. aureus*, *Vibrio cholerae*, *Shigella dysenteriae*, *Bacillus subtilis*, and *P. aeruginosa* (MIC of aqueous fraction = 3.125–25 mg/ml) [71]	The aqueous extract was relatively toxic in the acute toxicity test in Swiss Albino mice (LD_{50} = 489.9 mg/kg BW) [71]
31.	*Cymbopogon citratus* (DC.) Stapf	URT disorders	The oils are effective against *S. aureus*, *Bacillus cereus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, and *E. coli* (MIC 0.03–0.5 mg/ml) [72]	The oils were nontoxic to rats. They did not induce any adverse effects to the blood, liver function, kidney function, protein, carbohydrate, and lipid metabolism [73]
32.	*Citrus limon* (L.) Osbeck	URT disorders	The peel extract exhibited potent antibacterial effects against *S. aureus*, *B. subtilis*, *E. coli*, *K. pneumonia*, and, *Salmonella typhi* (MIC = 50–6.25 mg/ml) [74]	Essential oils are generally nontoxic and have classified as generally recognized as safe (GRAS) by the FDA [75]
33.	*Tinospora sinensis* (Lour.) Merr.	URT disorders	Antioxidant [76], immunostimulatory, analgesic, anti-inflammatory, and antimicrobial activities against *S. aureus* [77, 78]	No toxicity data available

both COX-2 and COX-1 *in vitro* with IC_{50} values of 13.33 ± 4.36 and 11.05 ± 1.43 μg/ml, respectively [137].

While *W. ugandensis* is widely used by herbalists in Uganda for treating various infections, it is also known to be toxic if used in high doses [80]. The acute toxicity evaluation of the aqueous stem bark extract of *W. ugandensis* in mice gave an LD_{50} >5000 mg/kg body weight with no mortalities recorded for all dose levels used. The extract was classified as

noncytotoxic with 50% cytotoxic concentration (CC_{50}) determined to be >250 μg/ml [138]. *W. ugandensis* was cytotoxic to intestinal epithelial cells IEC-6, with IC_{50} values <50 μg/ml [139]. Both the DMSO (CC_{50} = 1.5 μg/ml) and the ethanol (CC_{50} = 7.6 μg/ml) root were highly cytotoxic to U87CD4CXCR4 cells [140].

The evidence in the literature is not enough to draw conclusions on the usefulness of *W. ugandensis* in the

management of diseases of the respiratory tract or gastric ulcers. It can be toxic when used in high doses.

3.2.9. Zingiber officinale Roscoe (Zingiberaceae).

Zingiber officinale (ginger) is locally used as a constituent of syrups for the management of URTI including Yeco cough doctor® and Muwereza herbal cough remedy®.

Z. officinale contains various phytochemicals including phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers. The pharmacological activities of ginger have however been attributed to phenolic compounds such as gingerols and shogaols [141]. Various studies have demonstrated the anti-inflammatory activity of ginger and its bioactive compounds. Orally administered ginger reduced the proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and increased the anti-inflammatory cytokines (IL-10 and IL-22) in mouse colitis models [142]. *Z. officinale* attenuated post-exercise-induced elevation in several proinflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in well-trained male endurance runners [143].

Intravenous administration of 6-gingerol (at 1.75–3.5 mg/kg) and 6-shogaol (at 1.75–3.5 mg/kg) and oral administration of both (at 70–140 mg/kg) produced an inhibition of spontaneous motor activity, as well as antipyretic and analgesic effects, the latter producing more intense effects than the former. 6-Shogaol also showed an intense antitussive effect in comparison with dihydrocodeine phosphate [144]. This supports of the use of *Z. officinale* in herbal cough remedies for their cough-suppressant activity.

The ethanolic extract of *Z. officinale* rhizome was active against common respiratory tract pathogens: *S. aureus, S. pyogenes, S. pneumoniae*, and *Haemophilus influenzae* [145]. Furthermore, an herbal extract of *Z. officinale* inhibited biofilm formation and affected the membrane integrity of multidrug-resistant *P. aeruginosa*, both of which play a role in the mechanism of infection and antimicrobial resistance [146]. The crude and methanolic fraction of ginger reduced biofilm formation, inhibited glucan synthesis and adhesion, and downregulated the virulence genes in *S. mutans* [147].

The antiviral activity of ginger has been demonstrated in some viruses not specifically implicated in the causation of common URTI. Fresh *Z. officinale* dose-dependently inhibited human respiratory syncytial virus (HRSV) and induced plaque formation in human respiratory tract cell lines [148]. Fresh ginger also dose-dependently inhibited viral attachment and internalization and, at high concentration, stimulated mucosal cells to secrete interferon β (IFN-β) that possibly contributed to counteracting viral infection. Other studies have demonstrated antiviral activity of *Z. officinale* in hepatitis C virus (HCV) [149] and Chikungunya virus that causes an arthritogenic febrile illness [150].

Studies on the safety of different *Z. officinale* rhizome extracts showed no treatment-related signs of toxicity or mortality in any animals at tested doses [151–154]. One such study revealed a no-observed-adverse-effect level for a crude ethanolic extract of 5000 mg/kg body weight [151].

There is scientific evidence in support of the use of *Z. officinale* extracts in preparations for the management of upper respiratory tract diseases. The rhizome has been established to be safe.

3.2.10. Allium sativum L. (Amaryllidaceae).

From the survey, *Allium sativum* (garlic) is used in Jenacid negus® for the management of peptic ulcer disease and in Yeco cough doctor® for the management of URTI.

An aqueous garlic extract was bactericidal against 16 clinical isolates and three reference strains of *Helicobacter pylori*. The MIC_{90} of the extracts was 5 mg/ml, and the MBC was equal to, or twofold higher than, the MIC. Boiling the garlic extract lowered the efficacy twofold to fourfold the values of MIC and the MBC obtained with fresh extract [155]. Another study in which the aqueous garlic extract was standardized for its thiosulfinate concentration revealed an MIC of 40 μg/ml of thiosulfinate against *H. pylori* [156].

Orally administered *A. sativum* juice at 250 and 500 mg/kg in rats produced a gastric ulcer healing effect in acetic acid-induced chronic gastric ulcer. The extracts also produced a gastric antisecretory effect in pylorus-ligated rats; gastric cytoprotective effect in ethanol-induced and indomethacin-induced gastric ulcer; and a significant reduction in stress-induced gastric ulcers and cysteamine-induced duodenal ulcers with higher effectiveness at 250 mg/kg [157]. Furthermore, aqueous garlic extract increased the pH and reduced the volume of gastric juice in rats [158].

An ethanolic garlic extract was bactericidal against *S. pyogenes*, which is commonly implicated in bacterial URTI, with an MBC of 1 g/ml [159]. The antiviral activity of garlic has been demonstrated in the following viruses known to cause URTI in humans; adenovirus [160]; influenza A and influenza B virus [161, 162]; human rhinovirus-2 [163]; and measles virus, Newcastle disease virus, and parainfluenza virus-3 [164]. Garlic acts by blocking viral entry into host cells, inhibiting viral RNA polymerase, reverse transcriptase, DNA synthesis, and immediate-early gene 1 (IEG1) transcription, as well as through downregulating the extracellular-signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathway [164]. These activities can be important in the management of URTI of different etiologies.

The most commonly reported adverse effects of garlic in randomized clinical trials are garlic breath and gastrointestinal symptoms [165]. Allergic reactions have also been reported in case reports [166–168]; contact dermatitis [169] and drug-herb interactions have been reported in patients taking anticoagulant medication (warfarin) and those on antiretroviral therapy [170].

Scientific evidence supports the use of *A. sativum* in the management of upper respiratory tract conditions and in peptic ulcer disease. The plant can be used with caution as cases of allergic reactions have been reported.

3.2.11. Eucalyptus globulus Labill. (Myrtaceae).

Eucalyptus globulus is a constituent of Nana herbal mouth wash®, Princess pain balm®, Phycof cough syrup®, Focus herbal cough syrup®, Lucas syrup®, Kwesiima cough mixture®, Gabogola syrup®, and Sacco syrup®.

An essential oil blend of *E. globulus* with other oils was effective against fourteen Gram-positive and Gram-negative bacteria strains tested, including some antibiotic-resistant strains [171]. The organisms tested in the study included those implicated in causation of URTI; for example, *S. pyogenes*, *S. pneumoniae*, *Listeria monocytogenes*, and *S. aureus*. MICs ranged from 0.01% to 3%. The study also found the blend effective against H1N1 influenza virus, making it suitable for management of influenza and post-influenza bacterial pneumonia infections [171]. The anti-bacterial effect of *E. globulus* has also been demonstrated in the organisms causing dental caries especially *S. mutans* [172] and *Lactobacilli* [173, 174].

The essential oil of *E. globulus* exhibited analgesic and anti-inflammatory effects in mice and rat models [175]. The essential oil of *E. globulus* possesses central and peripheral analgesic effects as well as neutrophil-dependent and neutrophil-independent anti-inflammatory activities [175].

A eucalyptus oil water emulsion had an LD_{50} of 3811.5 mg/kg. The oil slowed growth of the male rats and damaged the liver and the kidneys at 792 and 1188 mg/kg BW after oral administration, respectively [176]. In another study, an LD_{50} of 1650 mg/kg in mice was determined. In addition, there was no abnormal skin reaction observed when a 5% ointment formulation was administered on the rats' skin, indicating the safety of *E. globulus* essential oil at a relatively lower concentration [177].

E. globulus is safe for use, at low concentrations, for the management of URTI and dental conditions.

Table 3 shows the evidence of safety and efficacy of the plant raw materials used to manufacture herbal products in Uganda.

3.3. Availability of Plant Monographs. We reviewed the WHO monographs, African Pharmacopoeia, and West African Pharmacopoeia to obtain information on the availability of monographs for the plants used to manufacture products in Uganda. Of the 33 plant materials, only ten (10) had monographs published by the WHO, ten (10) by the African Pharmacopoeia, and six (6) by the West African Pharmacopoeia. Nonetheless, *Aloe vera* (L.) Burm.f. (Asphodelaceae), *Azadirachta indica* A.Juss. (Meliaceae), *Zingiber officinalis* Roscoe (Zingiberaceae), and *Allium sativum* L. (Amaryllidaceae) had monographs published by all three authorities (Table 2). The folk and/or traditional uses in these pharmacopoeias are similar to the Ugandan manufacturers' as indicated on the product labels for most of the herbs. In addition to the traditional uses, the monographs reviewed also state the pharmacological evidence, plant parts of interest, methods for preparation, and quality control procedures. Therefore, these monographs can be adopted for routine quality control of the materials produced in Uganda.

Table 2 summarizes the availability of plant monographs in African Pharmacopoeia, West African Herbal Pharmacopoeia, and WHO monographs on selected herbal materials. The traditional indications are outlined as they are stated in the monographs for comparison with Ugandan

manufacturer indications of the products containing the plant materials to justify adaptability of the monographs.

4. Conclusion

Several *in vitro* and *in vivo* studies have been carried out to establish the safety and efficacy of the plants used for the management of different conditions. For all plant materials, there is some scientific evidence to support the use of the plants in the management of the conditions on the label claim. However, some of these studies lack specificity for the conditions on the label claim and therefore may not be confidently relied upon to support the use of the plant material. More specific bioassays are required in these cases to provide conclusive evidence. Also, studies in humans are few, and therefore, in most cases, results from animal models and human cell lines are extrapolated to humans. Some plant materials have specific dose-dependent toxicities and interactions that should concern the manufacturers and the regulatory authorities before approval of the products. Other plants' toxicity depends on the preparation method, yet there are no GMP requirements for herbal manufacture in Uganda. Pharmacovigilance efforts should be stepped up to identify toxicity cases and establish efficacy of the finished products. Plant monographs are urgently required to standardize uses, processing, and quality assurance of plant materials.

Data Availability

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This work was approved by the Mbarara University of Science and Technology, Research and Ethics Committee.

Consent

Not applicable

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

B.K. conceived the idea, drafted the proposal, and participated in procuring the herbal products and manuscript writing; L.K.B. analyzed the primary data; H.K., E. I. M., S.L., and G.A. reviewed the plant safety and efficacy literature and drafted the manuscript; and J.A., A.W., C.U.T., K.F., and P.E.O. reviewed and approved the proposal and the manuscripts.

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